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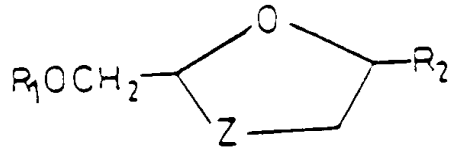
(54) Substituted -1,3-oxathiolanes with antiviral properties.

(57) Disclosed are compounds of the formula



wherein R_1 is hydrogen;
R_2 is a purine or pyrimidine base or an analogue or derivative thereof;
Z is S, S = O or SO_2; and
pharmaceutically acceptable derivatives thereof.
Also described are use of the compounds as antiviral agents, pharmaceutical formulations, and methods for the preparation of the compounds.

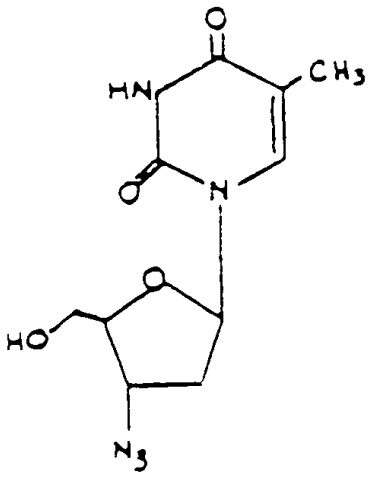
EP 0 382 526 A2

SUBSTITUTED-1,3-OXATHIOLANES WITH ANTIVIRAL PROPERTIES

The present invention relates to novel substituted 1,3-oxathiolane cyclic compounds having pharmacological activity, to processes for and intermediates of use in their preparation, to pharmaceutical compositions containing them, and to the use of these compounds in the antiviral treatment of mammals.

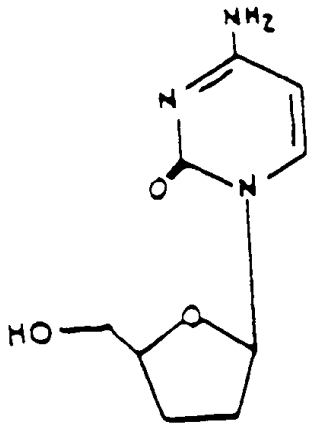
Retroviral infections are a serious cause of disease, most notably, the acquired immunodeficiency syndrome (AIDS). The human immunodeficiency virus (HIV) has been recognized as the etiologic agent of AIDS and compounds having an inhibitory effect against HIV multiplication have been actively sought.

Mitsuya et al., "3'-Azido-3'-deoxythymidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro", Proc. Natl. Acad. Sci. U.S.A., 82, pp. 7096-7100 (1985), refers to a compound of formula (A) (3'-azido-2',3'-dideoxythymidine), commonly referred to as AZT. This compound is said to be useful in providing some protection for AIDS carriers against the cytopathogenic effect of immunodeficiency virus (HIV).



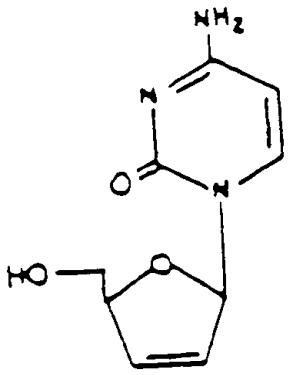
(A)

Mitsuya et al., "Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotrophic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxynucleosides", Proc. Natl. Acad. Sci. U.S.A., 86, pp. 1911-15 (1986), have also referred to a group of 2',3'-dideoxynucleosides shown in formula (B) which are said to possess protective activity against HIV-induced cytopathogenicity.



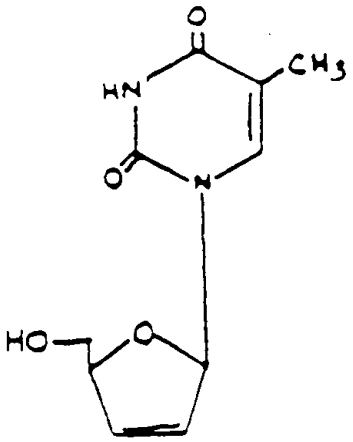
(B)

Balzarini et al., "Potent and selective anti-HTLV-III/LAV activity of 2',3'-dideoxycytidinene, the 2',3'-unsaturated derivative of 2',3'-dideoxycytidine", Biochem. Biophys. Res. Comm., 140, pp. 735-42 (1986), refer to an unsaturated analogue of these nucleosides--2',3'-dideoxy-cytidine, shown in formula (C)--as being characterized by antiretroviral activity.



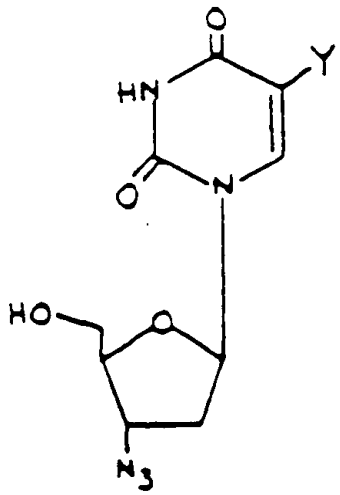
(C)

Baba et al., "Both 2',3'-dideoxythymidine and its 2',3'-unsaturated derivative (2',3'-dideoxythymidinene) are potent and selective inhibitors of human immunodeficiency virus replication in vitro", Biochem. Biophys. Res. Comm., 142, pp. 128-34 (1987), refer to the 2',3'-unsaturated analogue shown in formula (D) of 2',3'-dideoxythymidine. This analogue is purported to be a potent selective inhibitor of HIV replication.



(D)

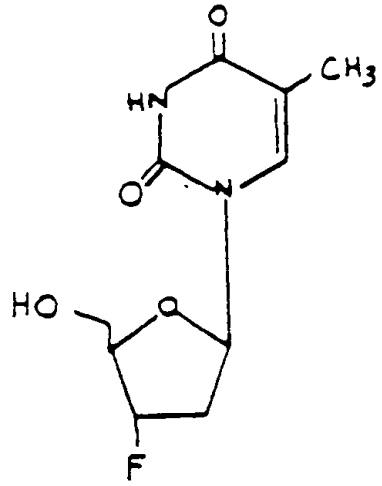
Analogues of AZT known as 3'-azido-2',3'-dideoxyuridine shown in formula (E), where Y is bromine or iodine, have been said to have an inhibitory activity against Moloney murine leukemia in T S. Lin et al., "Synthesis and antiviral activity of various 3'-azido, 3' amino, 2',3'-unsaturated and 2',3'- dideoxy analogues of pyrimidine, deoxyribonucleosides against retroviruses", J. Med. Chem., 30, pp. 440-41 (1987).



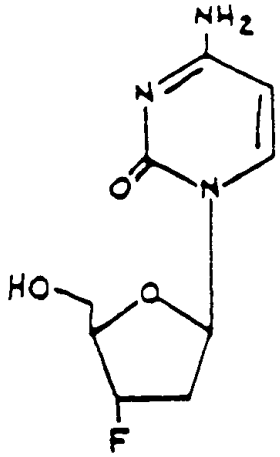
(E)

Finally, the 3'-fluoro analogues of 2',3'-dideoxycytidine shown in formula (F) and of 2',3'-dideoxythymidine shown in formula (G) are referred to in Herdewijn et al., "3'-Substituted 2',3'-dideoxynucleoside analogues as potential anti- HIV(HTLV-III/LAV) agents", J. Med. Chem., 30, pp. 1270-78 (1987), as having potent antiretroviral activity.

(F)



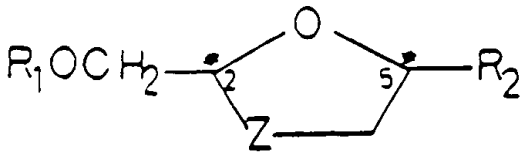
(G)



The most potent anti-HIV compounds thus far reported are 2',3'-dideoxynucleosides, more particularly, 2',3'-dideoxy cytidine (ddCyd) and 3'-azido-2',3'-dideoxythymidine (AzddThd or AZT). These compounds are also active against other kinds of retroviruses such as the Moloney murine leukemia virus. Because of the increasing incidence and the life-threatening characteristics of AIDS, efforts are being expended to discover and develop new non-toxic and potent inhibitors of HIV and blockers of its infectivity. It is therefore an object of the present invention to provide effective anti-HIV compounds of low toxicity and a synthesis of such new compounds that is readily feasible.

A structurally distinct class of compounds known as 2-substituted-5-substituted-1,3-oxathiolanes has now been discovered and found to have antiretroviral activity. In particular, these compounds have been found to act as non-toxic inhibitors of the replication of HIV-1 in T-lymphocytes over prolonged periods of time.

There is accordingly provided in a first aspect a compound of formula (I)



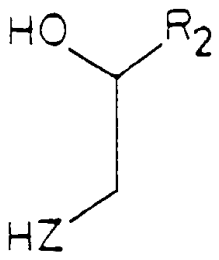
(I)

wherein R_1 is hydrogen;
R_2 is a purine or pyrimidine base or an analogue or derivative thereof;
Z is S, S=O or SO_2; and
pharmaceutically acceptable derivatives thereof.

It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least two chiral centers (shown as * in formula (I)) and thus exist in the form of two pairs of optical isomers (i.e. enantiomers) and mixtures thereof including racemic mixtures. Thus the compounds of formula (I) may be either cis isomers, as represented by formula (II), or trans isomers, as represented by formula (III), or mixtures thereof. Each of the cis and trans isomers can exist as one of two enantiomers or as mixtures thereof including racemic mixtures. All such isomers and mixtures thereof including racemic mixtures are included within the scope of the invention.

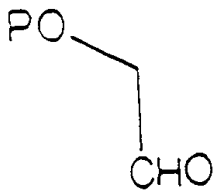
In a second process (B) one compound of formula (I) is converted to another compound of formula (I) by base interconversion. Such interconversion may be effected either by simple chemical transformation (e.g., the conversion of uracil base to cytosine) or by an enzymatic conversion using, for example, a deoxyribosyl transferase. Such methods and conditions for base interconversions are well known in the art of nucleoside chemistry.

In a third process (C) the compounds of formula (I) may be prepared by the reaction of a compound of formula (IX)



(IX)

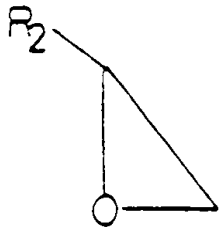
with a compound of formula (X)



(X)

where P is a protecting group, followed by removal of the protecting group.

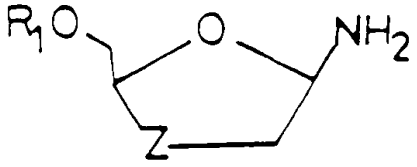
The compounds of formula (IX) may be prepared for reaction by a suitable epoxide (XI)



(XI)

with an appropriate sulphur-containing compound, e.g., sodium thioacetate. Compounds of formula (XI) are either known in the art or may be obtained by analogous processes.

In a fourth process (D) a compound of formula (XII)



(XII)

may be converted to a compound of formula (I) by conversion of the anomeric NH_2 group to the required base by methods well known in the art of nucleoside chemistry.

Many of the reactions described hereinabove have been extensively reported in the context of purine nucleoside synthesis, for example, in "Nucleoside Analogues - Chemistry, Biology and Medical Applications", R.T. Walker et al., Eds. Plenum Press, New York (1979) at pages 193-223, the text of which is incorporated by reference herein.

It will be appreciated that the above reactions may require the use of, or conveniently may be applied to, starting materials having protected functional groups, and deprotection might thus be required as an intermediate or final step to yield the desired compound. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g., benzyl), acyl or aryl (e.g., 2,4-dinitrophenyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene (John Wiley and Sons, 1981). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g., methyl, t-butyl or methoxymethyl), aralkyl (e.g., benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl, (e.g., acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g., t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g., by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g., by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved, for example, by treatment with BF_3 etherate and acetic anhydride followed by removal of acetate groups so formed at an appropriate stage in the synthesis. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride.

In the above processes the compounds of formula (I) are generally obtained as a mixture of the cis and trans isomers.

These isomers may be separated, for example, by acetylation, e.g., with acetic anhydride followed by separation by physical means, e.g., chromatography on silica gel and deacetylation, e.g., with methanolic ammonia or by fractional crystallization.

Pharmaceutically acceptable salts of the compounds of the invention may be prepared as described in United States Patent No. 4,383,114, the disclosure of which is incorporated by reference herein. Thus, for example, when it is desired to prepare an acid addition salt of a compound of formula (I), the product of any of the above procedures may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods. Pharmaceutically acceptable acid addition salts may be prepared by reacting the free base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g., ethyl acetate) or an alcohol (e.g., methanol, ethanol or isopropanol). Inorganic basic salts may be prepared by reacting the free base with a suitable base such as an alkoxide (e.g., sodium methoxide) optionally in the presence of a solvent such as an alcohol (e.g., methanol). Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compounds of formula (I) using conventional methods.

A compound of formula (I) may be converted into a pharmaceutically acceptable phosphate or other ester by reaction with a phosphorylating agent, such as $POCl_3$, or a suitable esterifying agent, such as an acid halide or anhydride, as appropriate. An ester or salt of a compound of formula (I) may be converted to the parent compound, for example, by hydrolysis.

Where the compound of formula (I) is desired as a single isomer it may be obtained either by resolution of the final product or by stereospecific synthesis from isomerically pure starting material or any convenient intermediate.

Resolution of the final product, or an intermediate or starting material therefore may be effected by any suitable method known in the art: see for example, Stereochemistry of Carbon Compounds, by E.L. Eliel (McGraw Hill, 1962) and Tables of Resolving Agents, by S.H. Wilen.

The invention will be further described by the following examples which are not intended to limit the invention in any way. All temperatures are in degrees celsius.

EXAMPLES

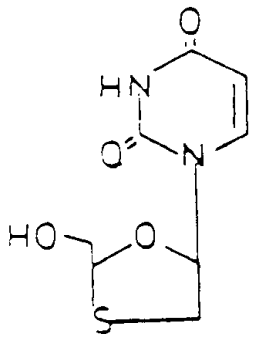
Example 1

2-thiobenzoyl acetaldehyde diethylacetal

7.71 (d, 1H, C_6-H cis, J = 8.2 Hz)
7.57 (m, 1H, aromatic)
7.45 (m, 3H, aromatic and N_3-H)
6.55 (dd, 1H, C_5-H trans, J = 2.4 and 5.4 Hz)
6.35 (dd, 1H, C_5-H cis, J = 4.1 and 5.6 Hz)
5.79 (t, 1H, C_2-H trans, J = 5.4 Hz)
5.73 (d, 1H, C_5-H trans, J = 8.2 Hz)
5.57 (d, 1H, C_5-H cis, J = 8.2 Hz)
5.46 (t, 1H, C_2-H cis, J = 3.9 Hz)
4.73 (d, 2H, $-CH_2\overline{O}-COC_6H_5$)
4.45 (t, 2H, $-CH_2OCOC_6H_5$)
3.57 (m, 1H, C_4-H)
3.17 (m, 1H, C_4-H)

Example 14

Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane



(XXIII)

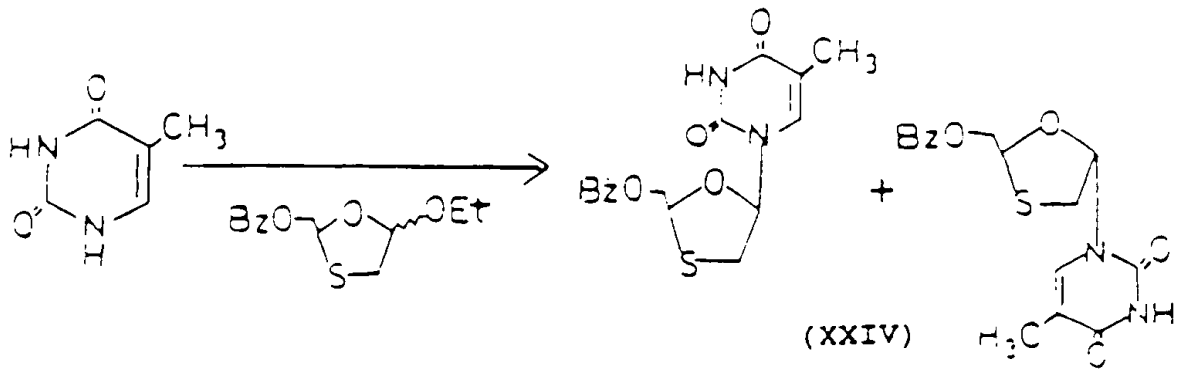
300 mg of a mixture cis- and trans-2-benzoyloxymethyl- 5-(uracil-N-1'-yl)-1,3-oxathiolanes was dissolved in 75 ml of methanolic ammonia. The mixture was stirred at room temperature overnight. The solution was evaporated by dryness. The residue was purified and the two isomers were separated on silica gel using EtOAc:MeOH 98:2 as eluant.

The top product was isolated as a solid product and was identified as cis-isomer.

Cis-isomer: m.p. 162-164° C; R_f: 0.57 in EtoAc:MeOH 95:5
U.V.: (MeOH) Lambda max: 261.4 nm
^{1}H-NMR δ(ppm in DMSO-d_6):
11.36 (s,1H, N_3-H)
7.88 (d, 1H, C_6-H, J = 8.1 Hz)
6.18 (t, 1H, C_5-H, J = 4.8 Hz)
5.62 (d, 1H, C_5-H, J = 8.1 Hz)
5.33 (t, 1H, C_2-H, J = 5.7 Hz)
5.17 (t, 1H, -OH, D_2O exchange)
3.72 (t, 2H, C_2-CH_2OH, J = 4.6 Hz)
3.41 (dd, 1H, C_4-H, J = 5.7 and 12 Hz)
3.20 (dd, 1H, C_4-H, J = 4.6 and 9.9 Hz)

Example 15

Cis- and trans-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolanes



(XXIV)

1.7 g of thymine was heated at reflux in 50 ml of HMDS containing 50 mg of $(NH_4)_2SO_4$ until the solution became clear. The mixture was evaporated under reduced pressure. The residue was dried under high vacuum for 1 hour and dissolved in 150 ml of 1,2-dichloroethane.

3 g of 2-benzoyloxymethyl-5-ethoxy-1,3-oxathiolane was dried by evaporation twice with 75 ml of benzene and dissolved in 150 ml of dry 1,2-dichloroethane.

The silylated thymine solution was transferred into the oxathiolane through a canula under argon atmosphere. 3.3 ml of TMS-Triflate (trimethylsilyltriflate) in 30 ml of dry 1,2-dichloroethane was introduced into the reaction mixture through a canula under argon atmosphere. The solution was heated at reflux under argon atmosphere for 36 hours, cooled to room temperature and poured into 300 ml of saturated aqueous $NaHCO_3$ solution. The organic layer was collected and the aqueous phase was extracted twice with methylene chloride (2 X 100 ml). The combined organic phase was washed twice with water (2 X 200 ml), once with NaCl solution (1 X 150 ml) and dried over $MgSO_4$. The solution was filtered. The filtrate was evaporated in vacuum. The residue was purified on silica gel using Hexane:EtOAc 1:1 as eluant. It yielded 1.3 g (35%) of pure product.

The product was shown as only one spot on TLC but the ^{1}H-NMR spectrum indicated the presence of the two isomers cis and trans in a ratio of 1:1.2.

R_f: 0.30 in Hexane:EtOAc 2:3

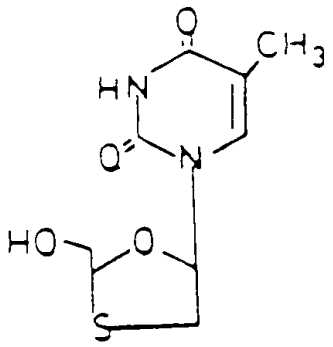
U.V.: (MeOH) Lambda max: 266 nm

^{1}H-NMR δ(ppm in $CDCl_3$):

8.60 (broad singlett, N_3-H)
8.06 (m, 2H, aromatic)
7.59 (m, 1H, aromatic)
7.49 (m, 2H, aromatic)
7.38 (d, 1H, C_6-H-cis, J = 1.3 Hz)
7.28 (d, 1H, C_6-H-trans, J = 1.3 Hz)
6.55 (dd, 1H, C_5-H-trans isomer, J = 3.1 and 5.6 Hz)
6.38 (t, 1H, C_5-H-cis isomer, J = 5.5 Hz)
5.78 (dd, 1H, C_2-H-trans, J = 4.4 and 6.4 Hz)
5.46 (t, 1H, C_2-H-cis-isomer, J = 4.3 Hz)
4.69 (d, 2H, C_2-$CH_2OCOC_6H_5$, J = 4.2 Hz)
4.45 (m, 2H, C_2-$CH_2OCOC_6H_5$)
3.58 (m, 1H, C_4-H)
3.13 (m, 1H, C_4-H)
1.93 (d, 1H, C_5-CH_3-trans isomer, J = 1.2 Hz)
1.78 (d, 1H, C_5-CH_3-cis isomers, J = 1.2 Hz)

Example 16

Cis-2-hydroxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolanes



(XXV)

500 mg of a mixture cis- and trans-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolanes (XXIV) was dissolved in 100 ml of saturated methanolic ammonia. The mixture was stirred at room temperature overnight (18 hours). The mixture was then evaporated to dryness under reduced pressure. The residue was separated on silica gel using EtOAc:MeOH 98:2 as eluant.

The less polar product was identified as cis-isomer mp: 167-168° C; R_f: 0.66 in EtOAc:MeOH 95.5

U.V.: (MeOH) Lambda max: 266 nm

^{1}H-NMR δ(ppm in DMSO-d_6)

11.38 (s, 1H, N_3'-H)

7.73 (d, 1H, C_6'-H, J = 1.1 Hz)

6.16 (t, 1H, C_5-H, J = 5.5 Hz)

5.31 (t, 1H, C_2-H, J = 5.9 Hz)

5.14 (t, 1H, OH, D_2O exchange)

3.70 (t, 2H, C_2-CH_2OH, J = 5.1 Hz)

3.36 (dd, 1H, C_4-H, J = 5.7 and 1.7 Hz)

3.16 (dd, 1H, C_4-H, J = 5.5 and 11.7 Hz)

1.75 (d, 3H, C_5'-CH_3, J = 1.7 Hz)

Example 17

Tablet Formulations

A. The following formulation is prepared by wet granulation of the ingredients with a solution of povidone in water, drying and screening, followed by addition of magnesium stearate and compression.

	mg/tablet
(a) Active ingredient	250
(b) Lactose B.P.	210
(c) Povidone B.P.	15
(d) Sodium Starch Glycollate	20
(e) Magnesium Stearate	5
	500

B. The following formulation is prepared by direct compression; the lactose is of the direct compression type.

	mg/tablet
Active ingredient	250
Lactose	145
Avicel	100
Magnesium Stearate	5
	500

C. (Controlled Release Formulation) The formulation is prepared by wet granulation of the ingredients (below) with a solution of povidone in water, drying and screening followed by the addition of magnesium stearate and compression.

	mg/tablet
(a) Active ingredient	500
(b) Hydroxypropylemethylcellulose (Methocel K4M Premium)	112
(c) Lactose B.P.	53
(d) Povidone B.P.	28
(e) Magnesium Stearate	7
	700

Example 18

Capsule Formulation

A capsule formulation is prepared by admixing the ingredients below and filling into a two-part hard gelatin capsule.

	mg/capsule
Active ingredient	125
Lactose	72.5
Avicel	50
Magnesium Stearate	2.5
	250

Example 19

Injectable Formulation

Active ingredient 0.200 g
Sodium hydroxide solution, 0.1M q.s. to a pH of about 11.
Sterile water q.s. to 10 ml.

The active ingredient is suspended in some of the water (which may be warmed) and the pH adjusted to about 11 with a solution of sodium hydroxide. The batch is then made up to volume and filtered through a sterilizing grade membrane filter into a sterile 10 ml glass vial and sealed with sterile closures and overseas.

Example 20

suppository

	mg/suppository
Active ingredient	250
Hard Fat. B.P.	1770
	2020

One-fifth of the hard fat is melted in a steam-jacketed pan at 45° C maximum. The active ingredient is sifted through a 200 µm sieve and added to the molten base with mixing, using a high shear stirrer, until a smooth dispersion is achieved. Maintaining the mixture at 45° C, the remaining hard fat is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a 250 µm stainless steel screen and, with continuous stirring, is allowed to cool to 40° C. At a temperature of 38° C to 40° C, 2.02 g of the mixture is filled into suitable, 2 ml plastic molds. The suppositories are allowed to cool to room temperature.

Example 21

Antiviral Activity

In vitro testing was conducted on several of the compounds of this invention to determine their inhibitory properties. The results are shown in Tables 1 and 2. The concentrations reported are µg/ml in the incubation media which affect the susceptibility of a continuous line of T-cells developed at the Lady Davis Institute for Medical Research (Montreal) by Dr. Mark A. Wainberg toward infection by HIV-1 following a protocol similar to that of H. Mitsuya and S. Broder, "Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxy nucleosides". Proc. Natl. Acad. Sci. USA. 83. pp. 1911-15 (1986). Protection of the cell line from infection was monitored by staining with monoclonal antibodies against viral proteins in the standard manner (Table 1). In all experiments, comparisons were made with the drug AZT as the control. In order to confirm the results, the drug effects were monitored by measuring reverse transcriptase (RT) activity in the U-937 line of human monocytic cells as assayed in the usual manner with tritiated thymidine triphosphate (TTP) (Table 2). Finally, the drug effects on cell viability as measured by the well-know cytolytic effects of HIV-1 on the MT-4 cell line was evaluated in the accepted manner (Table 1).

Toxicity

No toxic effects were observed in the above tests.

Table 1

Inhibition of HIV-1 product by compounds of formula (I) in MT-4 cells

a) Viable cell counts (6 days in culture) using 2 µg/ml of compound

Compound	Cell Viability %
no drug	6.47
AZT	88.6
cis-XVI	87.4
trans-XVI	24
cis-XVII(b)	14
cis-XXV	11
cis-XXI	18
cis-XXIII	14

b) P-24 immunofluorescence

Time in Culture		% Immunofluorescent Cells	
(Days)	No Drug	2µg/ml AZT	2µg/ml cis-XVI
3	5.9	1.0	1.0
6	99	1.0	7.6

c) Reverse transcriptase assay

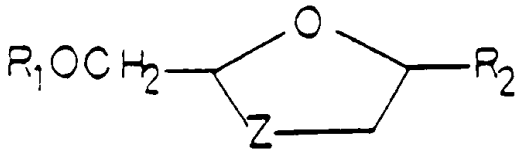
Time in Culture		RT Activity (CPM X 1000)/ml	
(Days)	No Drug	2µg/ml AZT	2µg/ml cis-XVI
3	36.43	1.564	2.381
6	339.0	1.748	2.301

Table 2

Inhibition of HIV-1 production by compounds of formula (I) in H-9 cells			
Reverse transcriptase assay			
Time in Culture		RT Activity (CPM X 1000)/ml	
(Days)	No Drug	2µg/ml AZT	2µg/ml cis-XVI
5	9.117	3.346	3.077
8	438.5	3.414	5.853
11	2550	2.918	3.560
14	2002	8.320	2.872
17	584.5	2.997	2.399
21	365.2	3.111	2.907
25	436.4	15.88	4.020
29	92.38	32.08	3.756
33	111.1	612.2	3.803
37	32.28	878.2	4.193
41	384.4	994.0	4.515
45	33.64	32.91	3.441

Claims

1. A 1,3-oxathiolane of formula (I), the geometric and optical isomers thereof, and mixture of those isomers:



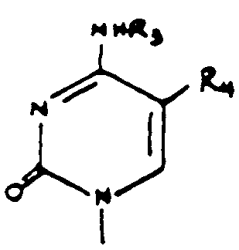
(I)

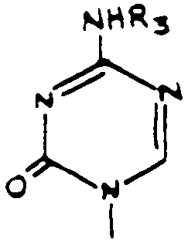
wherein:
R_1 is hydrogen;
R_2 is a purine or pyrimidine base or an analogue or derivative thereof;
Z is selected from a group consisting of S, S = O or SO_2; and
pharmaceutically acceptable derivatives thereof.

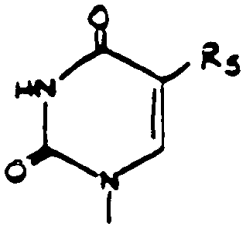
2. A compound of formula (I) as defined in claim 1 in the form of its cis isomer.

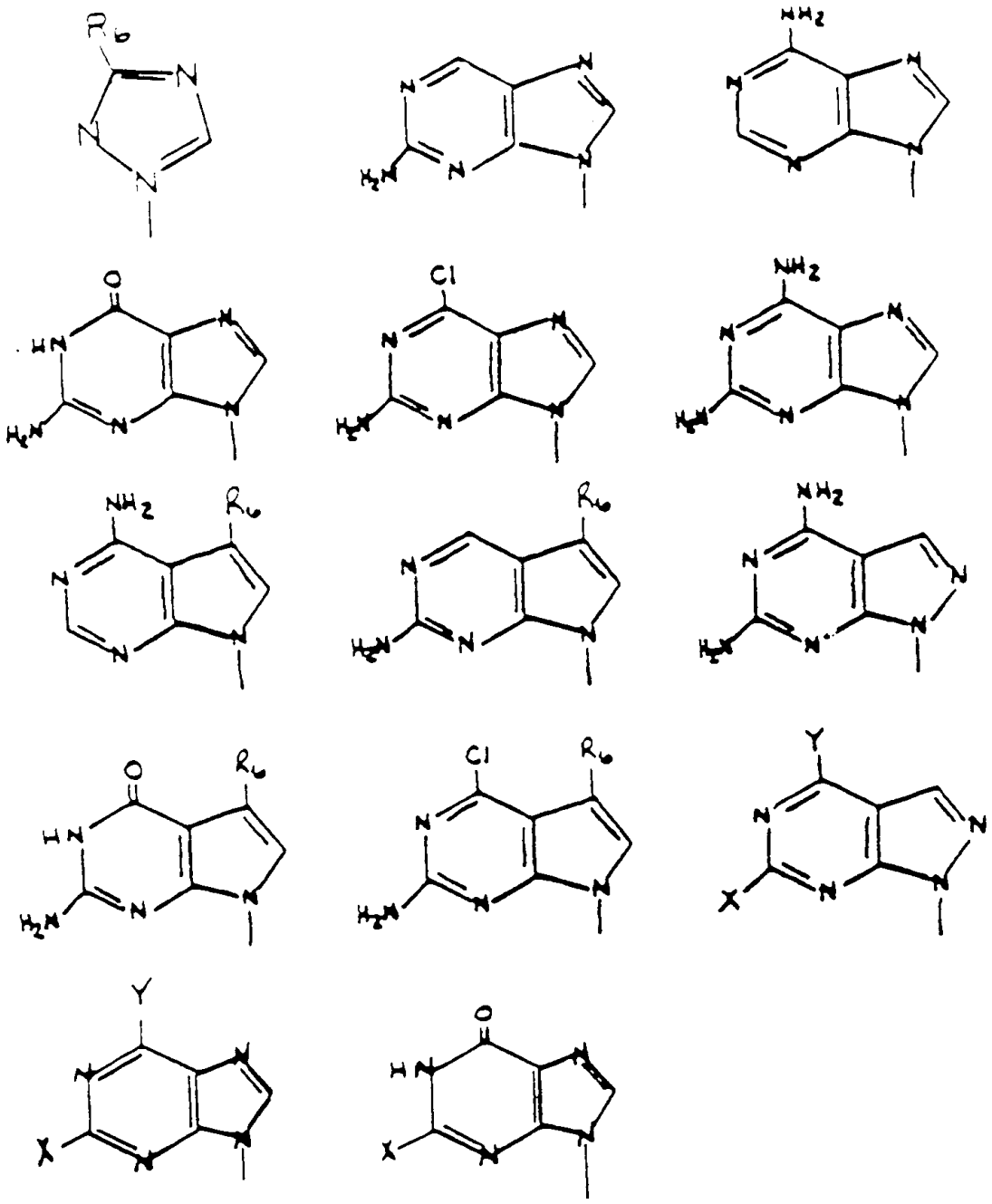
3. A compound of formula (I) as defined in claim 1 or claim 2 wherein Z is S.

4. A compound of formula (I) as defined in any one of claims 1 to 3 wherein R_2 is selected from:









wherein:

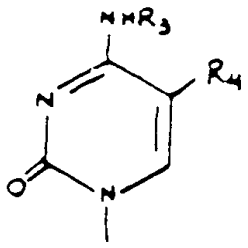
R_3 is selected from the group of hydrogen or C_{1-6} alkyl groups;

R_4 and R_5 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine;

R_6 is selected from the group of hydrogen, cyano, carboxy, ethoxycarbonyl, carbamoyl, or thiocarbamoyl; and

X and Y are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, amino or hydroxyl groups.

5. A compound according to any one of claims 1 to 4 wherein R_2 is



wherein R_3 is selected from the group of hydrogen or C_{1-5} alkyl groups and R_4 is selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-5} alkyl, bromine, chlorine, fluorine, or iodine.

6. A compound selected from the group consisting of:
Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(N_4'-acetylcytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-benzoyloxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof; and
Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane;
Cis-2-hydroxymethyl-5-(N-dimethylamino-methylene cytosin-1'-yl)-1,3-oxathiolane;
Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane;
and pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

7. Cis - 2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and pharmaceutically acceptable derivatives thereof.

8. A compound according to any one of claims 1 to 7 in the form of a racemic mixture.

9. A compound according to any one of claims 1 to 7 substantially in the form of a single enantiomer.

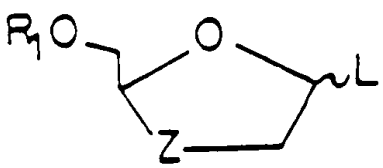
10. A compound of formula (I) as defined in any one of claims 1 to 9 or a pharmaceutically acceptable derivative thereof for use as an active therapeutic agent.

11. A compound of formula (I) as defined in any one of claims 1 to 9 or a pharmaceutically acceptable derivative thereof for use in the manufacture of a medicament for the treatment of a viral infection.

12. A pharmaceutical formulation comprising a compound of formula (I) as defined in any one of claims 1-9 or a pharmaceutically acceptable derivative thereof together with a pharmaceutically acceptable carrier therefor.

13. A pharmaceutical formulation according to claim 12 additionally comprising a further therapeutic agent.

14. A 1,3-oxathiolane of formula (VIII), the geometric and optical isomers thereof, and mixtures of those isomers:

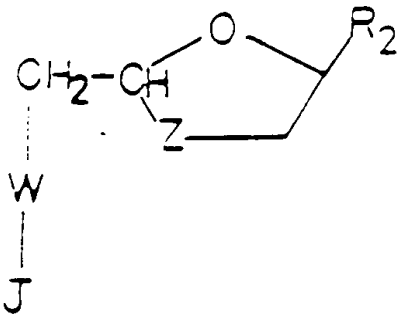


(VIII)

wherein:

R_1 is hydrogen or a hydroxyl protecting group; and
L is an alkoxy carbonyl group, iodine, bromine, chlorine or -OR where R is selected from the group consisting of a substituted or unsubstituted, saturated or unsaturated alkyl group and a substituted or unsubstituted, saturated or unsaturated aliphatic or aromatic acyl group.

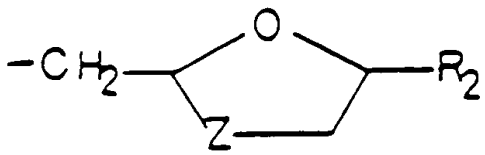
15. The ester of formula (IV) the geometric and optical isomers thereof, and mixtures of those isomers:



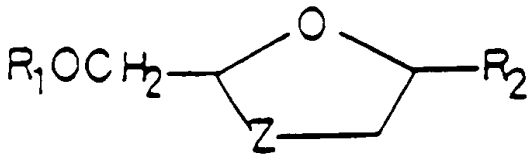
(IV)

wherein:
W is PO_4^-, SPO_3^- or
-O- C -$(CH_2)_n$- C -O- where n is an integer of 1 to 10;
J is any nucleoside or nucleoside analog or derivative thereof;
Z is S, S = O, or SO_2; and
R_2 is a purine or pyrimidine base or analogue or derivative thereof.

16. A compound according to claim 15 wherein J is:

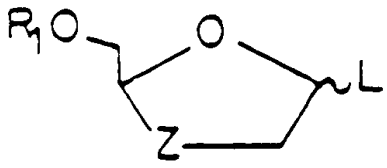


17. A process for the preparation of a compound of formula (I)



(I)

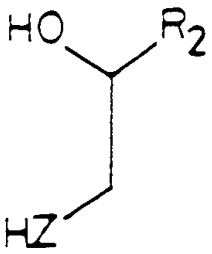
wherein R_1 is hydrogen;
R_2 is a purine or pyrimidine base or an analogue or derivative thereof;
Z is S, S = O or SO_2; and
pharmaceutically acceptable derivatives thereof, which comprises:
(a) reaction of a compound of formula (VIII)



(VIII)

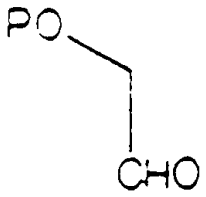
wherein R_1 is hydrogen or a hydroxyl protecting group and L is a displaceable atom or a group with a base

R_2-H group:
(b) base interconversion of one compound of formula (I) into another compound of formula (I);
(c) reaction of a compound of formula (IX)



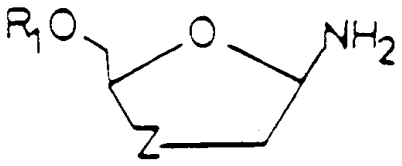
(IX)

with a compound of formula (X)



(X)

wherein P is a protecting group; or
(d) conversion of a compound of formula (XII)



(XII)

to a compound of formula (I)
and if necessary or desired subjecting the compound resulting from any of steps (a) to (d) to one or two further reactions comprising:

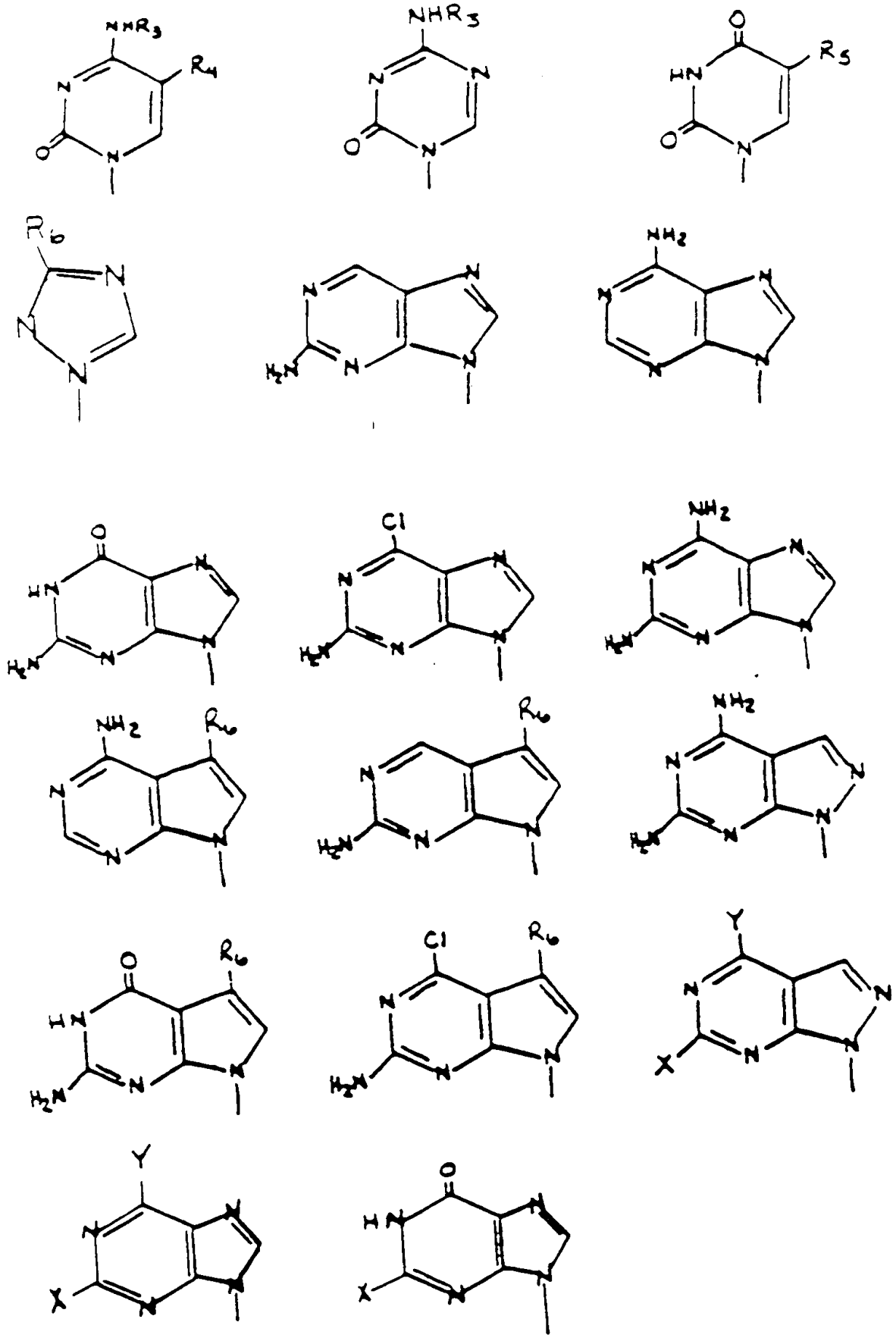
(i) removing any protecting groups;

(ii) converting a compound of formula (I) or a salt thereof into a pharmaceutically acceptable salt thereof.

18. A process as defined in claim 17 wherein the compound of formula (I) is obtained in the form of its cis isomer.

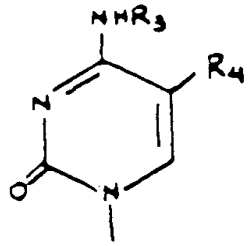
19. A process according to claim 17 or claim 18 wherein Z is S.

20. A process according to any one of claims 17 to 19 wherein R_2 is:



wherein:
R_3 is selected from the group of hydrogen, trifluoromethyl or saturated or unsaturated C_{1-5} alkyl groups;
R_4 and R_5 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-5} alkyl, bromine, chlorine, fluorine, or iodine;
R_5 is selected from the group of hydrogen, cyano, carboxy, ethoxycarbonyl, carbamoyl, or thiocarbamoyl; and
X and Y are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, amino or hydroxyl groups.

21. A process according to any of claims 17 to 19 wherein R_2 is:



wherein R_3 is selected from the group of hydrogen, trifluoromethyl or saturated or unsaturated C_{1-5} alkyl groups and R_4 is selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-5} alkyl, bromine, chlorine, fluorine, or iodine.

22. A process according to any one of claims 17 to 21 wherein the compound of formula (I) is selected from:
Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-benzoyloxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof; and
Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane;
Cis-2-hydroxymethyl-5-(N-dimethylamino-methylene cytosin-1'-yl)-1,3-oxathiolane;
Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane; trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane;
and pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

23. A process according to any one of claims 17 to 21 wherein the compound of formula (I) is Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and pharmaceutically acceptable derivatives thereof.

24. A process according to any one of claims 17 to 23 wherein the compound of formula (I) is obtained in the form of a racemic mixture.

25. A process according to any one of claims 1 to 7 wherein the compound of formula (I) is obtained substantially in the form of a single enantiomer.

26. A process according to any one of claims 17 to 25 wherein in step (a) the group L is selected from a group consisting of alkoxy carbonyl, iodine, bromine, chlorine or -OR, where R is a substituted or unsubstituted, saturated or unsaturated alkyl group or R is a substituted or unsubstituted aliphatic or aromatic acyl group.

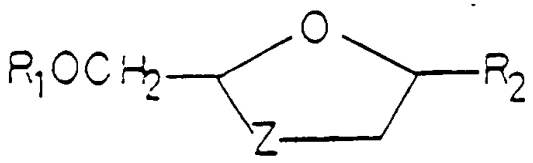
27. A process according to any one of claims 17 to 26 wherein step (a) the compound of formula (VIII) is reacted with a silylated purine or pyrimidine base in a compatible solvent in the presence of a Lewis acid

or trimethylsilyltriflate.

28. A method for the preparation of a pharmaceutical formulation comprising admixing a compound of formula (I) as defined in claim 17 or a pharmaceutically acceptable derivative thereof with a pharmaceutically acceptable carrier therefor.

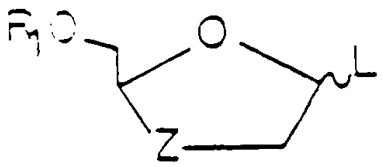
Claims for the following Contracting States: GR, ES

1. A process for the preparation of a compound of formula (I)



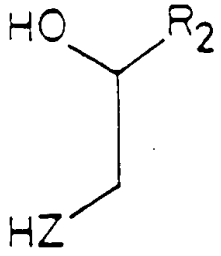
(I)

wherein R_1 is hydrogen;
R_2 is a purine or pyrimidine base or an analogue or derivative thereof;
Z is S, S=O or SO_2; and
pharmaceutically acceptable derivatives thereof, which comprises:
(a) reaction of a compound of formula (VIII)



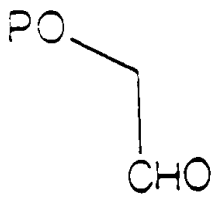
(VIII)

wherein R_1 is hydrogen or a hydroxyl protecting group and L is a displaceable atom or a group with a base R_2-H group;
(b) base interconversion of one compound of formula (I) into another compound of formula (I);
(c)reaction of a compound of formula (IX)



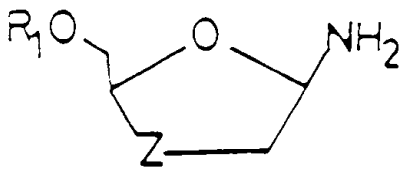
(IX)

with a compound of formula (X)



(X)

wherein P is a protecting group; or
(d) conversion of a compound of formula (XII)



(XII)

to a compound of formula (I)

and if necessary or desired subjecting the compound resulting from any of steps (a) to (d) to one or two further reactions comprising:

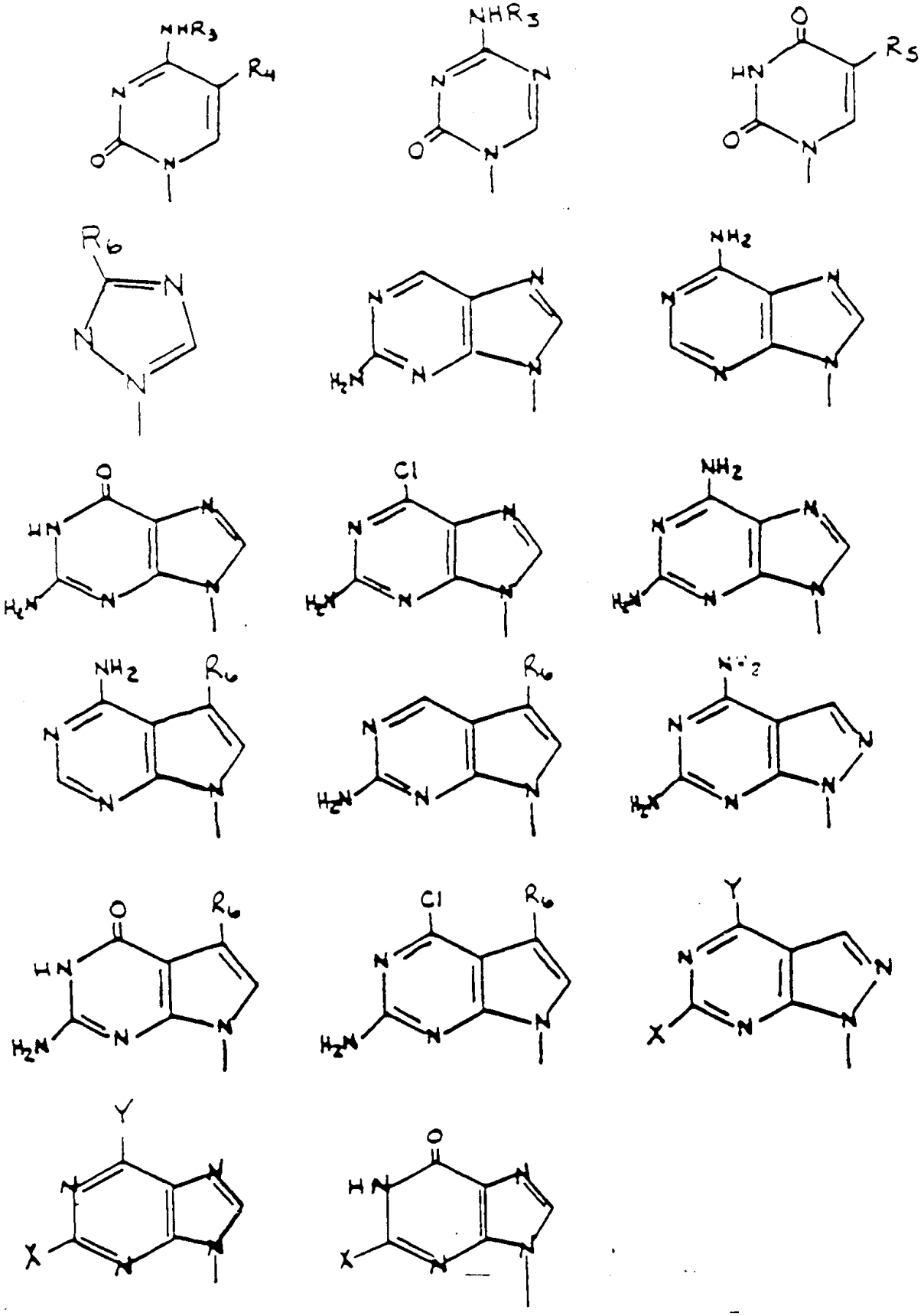
(i) removing any protecting groups;

(ii) converting a compound of formula (I) or a salt thereof into a pharmaceutically acceptable salt thereof.

2. A process as defined in claim 1 wherein the compound of formula (I) is obtained in the form of its cis isomer.

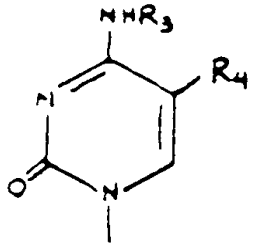
3. A process according to claim 1 or claim 2 wherein Z is S.

4. A process according to any one of claims 1 to 3 wherein R_2 is:



wherein
R_2 is selected from the group of hydrogen, trifluoromethyl or saturated or unsaturated C_{1-6} alkyl groups;
R_4 and R_5 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine;
R_6 is selected from the group of hydrogen, cyano, carboxy, ethoxycarbonyl, carbamoyl, or thiocarbamoyl; and
X and Y are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, amino or hydroxyl groups.

5. A process according to any of claims 1 to 3 wherein R_2 is:



wherein R_3 is selected from the group of hydrogen, trifluoromethyl or saturated or unsaturated C_{1-6} alkyl groups and R_4 is selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-6} alkyl, bromine, chlorine, fluorine, or iodine.

6. A process according to any one of claims 1 to 5 wherein the compound of formula (I) is selected from:
Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-benzoyloxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof; and
Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane;
Cis-2-hydroxymethyl-5-(N-dimethylamino-methylene cytosin-1'-yl)-1,3-oxathiolane;
Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane; trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane;
and pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

7. A process according to any one of claims 1 to 5 wherein the compound of formula (I) is Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and pharmaceutically acceptable derivatives thereof.

8. A process according to any one of claims 1 to 7 wherein the compound of formula (I) is obtained in the form of a racemic mixture.

9. A process according to any one of claims 1 to 7 wherein the compound of formula (I) is obtained substantially in the form of a single enantiomer.

10. A process according to any one of claims 1 to 9 wherein in step (a) the group L is selected from a group consisting of alkoxy carbonyl, iodine, bromine, chlorine or -OR, where R is a substituted or unsubstituted, saturated or unsaturated alkyl group or R is a substituted or unsubstituted aliphatic or aromatic acyl group.

11. A process according to any one of claims 1 to 10 wherein step (a) the compound of formula (VIII) is reacted with a silylated purine or pyrimidine base in a compatible solvent in the presence of a Lewis acid or